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(54) Title: PROCESS FOR PRODUCTION OF DEOXYGALACTONOJIRIMYCIN DERIVATIVES

(57) Abstract: A process for production of N-substituted-deoxygalactonojirimycin derivatives comprising reductive ring closure, followed by deprotection.

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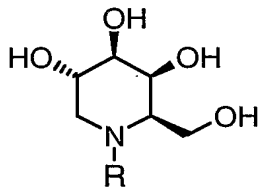
PROCESS FOR PRODUCTION OF DEOXYGALACTONOJIRIMYCIN DERIVATIVES

This invention relates to a process for production of N-substituted-deoxygalactonojirimycin derivatives and intermediates for use in said process.

US 6,291,657 discloses N-alkyldeoxygalactonojirimycin derivatives, including N-butyldeoxygalactonojirimycin (NB-DGJ) and their use as inhibitors of glycolipid synthesis. The preparation of NB-DGJ by reaction of deoxygalactonojirimycin with butyraldehyde under a hydrogen atmosphere with a palladium black catalyst is described. The process to the deoxygalactonojirimycin intermediate is not suitable for the large scale commercial preparation of NB-DGJ, for example in the quantities and purity required for use as a pharmaceutical. Therefore, improved processes for the production of NB-DGJ and other N-alkyldeoxygalactonojirimycin derivatives are required.

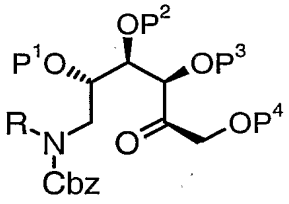
The present invention provides an improved process for the production of N-substituted-deoxygalactonojirimycin derivatives.

Thus according to the invention there is provided a process for the production of a compound of formula (I):



(I)

wherein R is C_{3-16} straight or branched chain alkyl, optionally substituted by C_{3-7} cycloalkyl, and optionally interrupted by -O-, the oxygen being separated from the ring nitrogen by at least two carbon atoms; or C_{1-10} alkylaryl where aryl is phenyl, optionally substituted by one or more substituents selected from F, CF_3, OCF_3, OR^1, and C_{1-6} straight or branched-chain alkyl; where R^1 is hydrogen, or C_{1-6} straight or branched-chain alkyl; which process comprises reductive ring closure of a compound of formula (II):



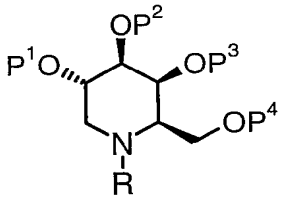
(II)

wherein R is defined for formula (I), and P^1 to P^4, which may be the same or different, are benzyl, substituted benzyl or benzylidene protecting groups, followed by deprotection to give the compound of formula (I).

Cbz is the group $PhCH_2OCO$-.

In the compounds of formula (I) R is preferably C_{3-16} straight or branched chain alkyl, more preferably R is C_{3-6} alkyl, in particular R is n-butyl.

The intermediate compound of formula (III):



(III)

wherein R is as defined for formula (I) and P^1 to P^4 are as defined for formula (II), which is formed following reductive ring closure of the compound of formula (II) may or may not be isolated from the reaction mixture. It is preferred that the compound of formula (III) is not isolated but is directly deprotected to give the compound of formula (I), however the reaction mixture may be filtered before the deprotection step. To reduce the formation of unwanted by-products it is preferable that the life-time of the imine produced following removal of the Cbz group from the compound of formula (II) is as short as possible.

Following deprotection, the compound of formula (I) may be purified by methods known to those skilled in the art such as using an anion exchange resin, crystallisation and/or chromatography e.g. cation exchange chromatography. Crystallisation of the compound of formula (I) is preferably from a mixture of water and acetone.

To aid in the work-up of the final compound butyraldehyde e.g. in an amount of 0.01 to 0.5, preferably 0.01 to 0.1 mole equivalents may be added to the reaction mixture after the reductive ring closure step.

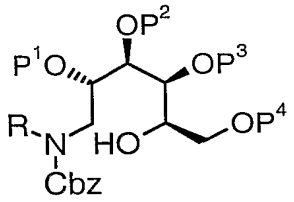
The compound produced according to the process of the invention is preferably obtained with a purity of >95%, more preferably >99% w/w.

Protecting groups P^1 to P^4 are preferably the same. Preferred protecting groups for use in the invention are benzyl or substituted benzyl, more preferably benzyl. When P^1 to P^4 are benzyl deprotection is preferably conducted in the presence of hydrogen gas and a catalyst such as $PdCl_2$ or palladium on carbon in a suitable solvent such as an alcohol, e.g. ethanol or preferably methanol. Substituted benzyl protecting groups which may be used include p-methoxybenzyl. Two adjacent P^1 to P^4 groups may be a benzylidene protecting group, e.g. P^1 and P^2 may be benzylidene.

It will be appreciated that following the synthesis of the compound of formula (I) further functional group conversions may be performed e.g. to change the nature of the R group or to convert it to hydrogen.

The reductive ring closure of the compound of formula (II) may be conducted under any suitable reducing conditions known to those skilled in the art, for example in the presence of hydrogen gas and a catalyst such as palladium on carbon e.g. 10% palladium on carbon, in a suitable solvent such as an alcohol, e.g. ethanol or preferably methanol.

The compounds of formula (II) may be produced by oxidation of a compound of formula (IV):

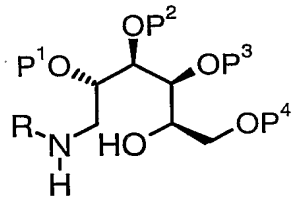


(IV)

wherein R is as defined for formula (I) and P^1 to P^4 are as defined for formula (II).

Any suitable oxidising agent known to those skilled in the art may be used. Suitable oxidising agents include trichloroisocyanuric acid in the presence of a catalyst e.g. 1,1',6,6'-tetramethyl piperidine-1-oxyl (TEMPO) in a suitable solvent such as sodium acetate / isopropyl acetate or sodium acetate / acetone, preferably at reduced temperature e.g. about -5 to 5°C, such as about -5 to 0°C or about 0 to 5°C. Alternative oxidising agents include iodoxybenzoic acid in DMSO.

The compounds of formula (IV) may be produced by reaction of a compound of formula (V):



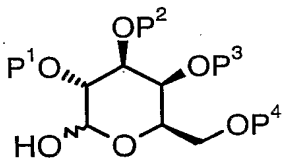
(V)

wherein R is as defined for formula (I) and P^1 to P^4 are as defined for formula (II), with a compound of formula (VI):

Cbz-L (VI)

wherein L is a leaving group, for example chloro, in a suitable solvent e.g. isopropyl acetate or dichloromethane.

The compounds of formula (V) may be produced by reductive amination of the corresponding protected D-galactopyranose of formula (VII):



(VII)

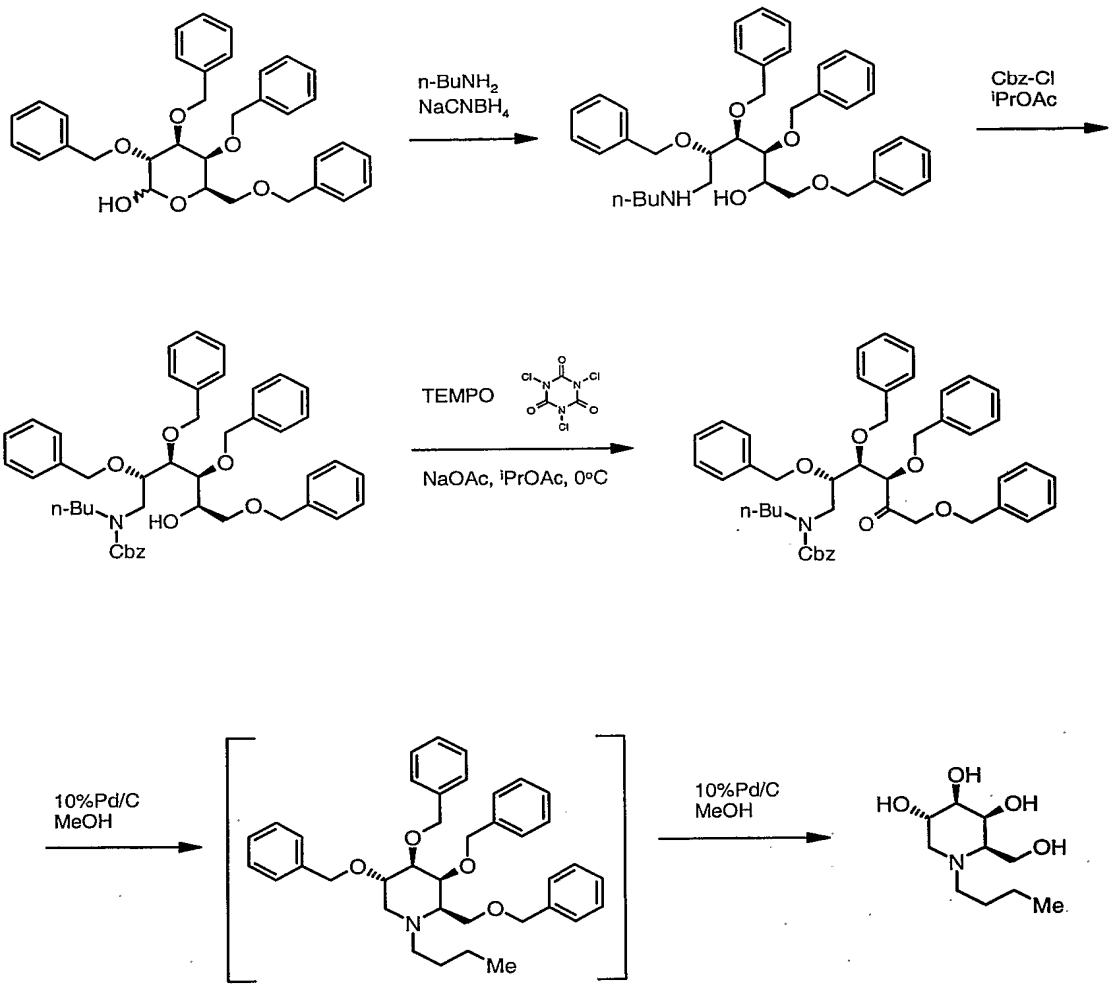
wherein P^1 to P^4 are as defined for formula (II), with a compound of formula (VIII):

$R\text{-}NH_2$ (VIII)

wherein R is as defined for formula (I). The reductive amination is preferably conducted in the presence of sodium cyanoborohydride. Preferably at elevated temperature, e.g. about 50°C.

The compounds of formulae (VI), (VII) and (VIII) are commercially available or may be prepared by methods known to those skilled in the art.

Scheme 1 below shows the synthesis of the compound N-butyldeoxygalactonojirimycin from 2,3,4,6-tetra-O-benzyl-D-galactopyranose according to the method of the invention:



Scheme 1

Further details for the preparation of compounds of formula (I) according to the method of the invention are found in the examples.

Any novel intermediate compounds as described herein also fall within the scope of the present invention.

Thus according to a further aspect of the invention there is provided a compound of formula (II), (IV) or (V) as defined above.

The compounds of formula (I) produced according to the method of the invention may be formulated as pharmaceutical compositions, e.g. for oral administration, by mixing with a pharmaceutically acceptable carrier.

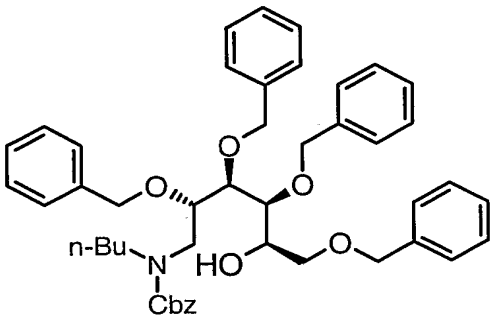
All publications, including, but not limited to, patents and patent applications, referred to in this application, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Example 1

Synthesis of N-butyldeoxygalactonojirimycin (I)

a)



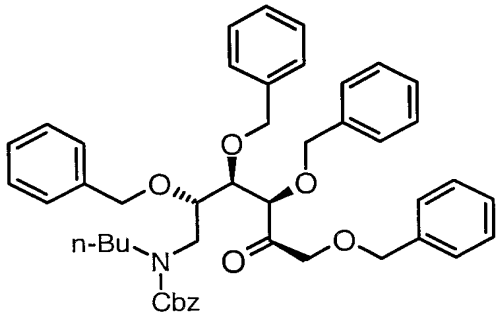
The reactor was loaded with 2,3,4,6-tetra-O-benzyl-D-galactopyranose (540.65 g, 1.00 mol) and sodium cyanoborohydride (69.12 g, 1.1 mol) under an atmosphere of nitrogen. Methanol (1500 mL) and n-butylamine (198.48 mL, 2.0 mol) were added. A mixture of acetic acid (228.72 mL, 4.0 mol) and methanol (300 mL) were added over 30 min at 20-25°C to the yellow solution. Caution: Evolution of hydrogen. The internal temperature was slowly raised to 50°C over 60 min. The reaction mixture was stirred at this temperature until tlc showed the complete consumption of the starting material (about 6-12 h). 1N NaOH (2000 mL) was slowly added to the mixture at 18-25°C. The reaction mixture was extracted with methylene chloride (3 x 600 mL). The combined organic layers washed with water (3 x 800 mL) to give the intermediate of formula (V) where R = butyl and P^1 to P^4 = benzyl.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 – 7.34 (m, 20H, 4 x Ph), 4.37 – 4.76 (m, 8H, 4 x CH_2Ph), 3.78 – 4.04 (m, 4H), 3.47 – 3.55 (m, 2H), 2.37 – 2.88 (m, 4H), 1.33 – 1.38 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.21 – 1.31 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.87 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$).

Saturated sodium bicarbonate solution (2000 mL) was added to the methylene chloride solution. Benzyl chloroformate (148.04 mL, 1.05 mol) was added slowly over 30 min and the mixture vigorously stirred for 1-2 h until tlc showed complete conversion. The layers were separated. The organic layer was stirred with 30% NaOH (44 mL) for at least 30 min and then diluted with water (960 mL). The organic layer was separated and washed with 1N HCl (1000 mL), sat. NaCl (1000 mL) and water (1000 mL). The resulting intermediate of formula (IV) where R = butyl and P^1 to P^4 = benzyl was kept in solution for the next step.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 – 7.41 (m, 25H, 5 x Ph), 4.99 – 5.17 (m, 2H, $COOCH_2$Ph), 4.38 – 4.74 (m, 8H, 4 x CH_2Ph), 3.12 – 4.12 (m, 10H), 1.36 – 1.44 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.13 – 1.27 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.80 – 0.88 (m, 3H, $CH_2CH_2CH_2CH_3$).

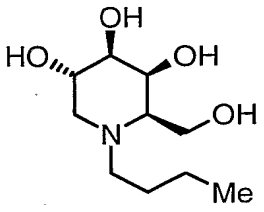
b)



A solution of the product from step a) (731.92 g, 1.00 mol) in methylene chloride was concentrated to about 50% of its volume at 300-750 mbar and a jacket temperature of 40-50°C. Methylene chloride (950 mL) was added and the solution concentrated again to 50% of its starting volume. The resulting solution was diluted with acetone (1250 mL) and concentrated to about 1.8 L/mol at p = 100-300 mbar. The reactor was dried under reduced pressure and loaded with sodium acetate (164.06 g, 2.0 mol) and TEMPO (15.63 g, 0.1 mol) at 0-2°C. The solution of the starting material was added after the reactor had been flooded with nitrogen. A solution of trichloroisocyanuric acid (104.58 g, 0.45 mol) in acetone (420 mL) was added slowly over at least 8 h at 0-2°C. After tlc showed complete conversion, the reaction mixture was filtered and washed with TBME (400 mL). Filtrate and washings were diluted with water (1200 mL) and extracted with TBME (1200 mL, 400 mL). The combined organic layers were washed with 1M HCl (1000 mL) and water (2 x 1000 mL). Yield of intermediate (II) of formula where R = butyl and P^1 to P^4 = benzyl >85%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 – 7.48 (m, 25H, 5 x Ph), 4.97 – 5.17 (m, 2H, $COOCH_2Ph$), 4.18 – 4.70 (m, 8H, 4 x CH_2Ph), 3.01 – 4.08 (m, 9H), 1.31 – 1.46 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.10 – 1.28 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.78 – 0.87 (m, 3H, $CH_2CH_2CH_2CH_3$).

c)



Charcoal (30 g) was added to the solution of the product of step b) (729.90 g, 1.00 mol) in TBME. The mixture was concentrated to a volume of about 1.5 L at 100-500 mbar and a jacket temperature of 40-50°C. This mixture was diluted with methanol (2500 mL) and concentrated again to a volume of about 1.5 L. The mixture was filtered and washed with methanol (1500 mL). Filtrate and washings were further diluted with methanol (5000 mL). The dry and inert reactor was loaded with 10% Pd/C (e.g. Johnson Matthey type 490 paste 10%, water content ca. 60%: 73 g dry weight, 1% w/w). The methanolic solution of the product of step b) was added and the mixture stirred under hydrogen (1000-1300 mbar) at 18-25°C until the consumption of hydrogen had ceased (ca. 4-10 h). After tlc showed consumption of the starting material, the mixture was filtered and washed with methanol (400 mL). Filtrate and washings were concentrated to about 1.5 L at a jacket temperature of 40-60°C and 80-300 mbar. The solution was diluted with TBME (1700 mL), filtered over a plug of silica gel (750 g) and washed with TBME (2800 mL). Filtrate and washings were combined and concentrated to about 1 L at a jacket temperature of 40-60°C and 80-300 mbar. The residue was diluted with methanol (6 mL/g, the amount of the intermediate of formula (III) where R = butyl and P^1 to P^4 = benzyl was determined by LOD, all following amounts are valid for 1 mol of (III), recovery of the plug-filtration ca. 85%). The dry and inert reactor was loaded with palladium chloride (88.66 g) and methanol (200 mL) at 2-5°C. The methanolic solution of intermediate (III) was added with stirring. The reactor was flooded with nitrogen three times and the mixture stirred under an atmosphere of hydrogen for at least 12 h. The mixture is filtered after tlc shows complete

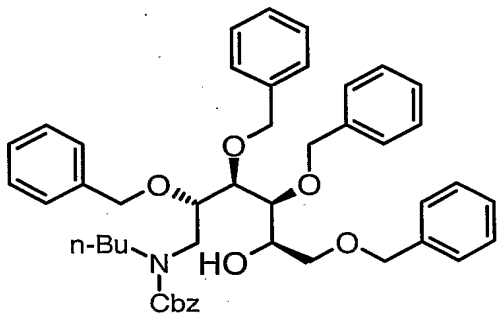
conversion and washed with methanol (200 mL). Caution: The filter cake is pyrophoric and must be kept wet with water. Filtrate and washings were slowly passed through a bed of basic ion exchanger (ca. 2 L wet, hydroxide form e.g. Amberlite IRA 400). The pH of the solution had to be ≥ 8 after leaving the column. Finally, the resin was washed with methanol (2000 mL). This solution was concentrated to about 500 to 750 mL. Charcoal (10 g) was added. The mixture was filtered (0.2 μm), concentrated to dryness and acetone (1300 mL) added. The mixture was heated to reflux and water (about 35 mL) was added until a clear solution was obtained. More acetone (1300 mL) was added and the resulting suspension cooled to 0°C over 3 h, filtered, the residue washed with acetone (300 mL) and dried at 35-45°C and 1 to 50 mbar to give 120-150g of the title compound as a white to off-white powder.

^{1}H NMR (D_2O): δ 4.07 (dd, J = 1.7 & 3.4 Hz, 1H), 3.86 (dd, J = 11.5 & 4.5 Hz, 1H), 3.85 (ddd, J = 9.7, 10.7 & 5.0 Hz, 1H), 3.78 (dd, J = 11.5 & 6.7 Hz, 1H), 3.39 (dd, J = 3.4 & 9.7 Hz, 1H), 3.02 (dd, J = 11.4 & 5.0 Hz, 1H), 2.67 (ddd, J = 13.5, 10.2 & 6.1 Hz, 1H, $CH_2CH_2CH_2CH_3$), 2.50 (ddd, J = 6.7, 4.5 & 1.7 Hz, 1H) 2.50 (ddd, J = 13.5, 10.5 & 5.5 Hz, 1H, $CH_2CH_2CH_2CH_3$), 2.21 (dd, J = 11.4 & 10.7 Hz, 1H), 1.46 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.27 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.90 (t, J = 7.4 Hz, 3H, $CH_2CH_2CH_2CH_3$).

Example 2

Synthesis of N-butyldeoxygalactonojirimycin (II)

a)



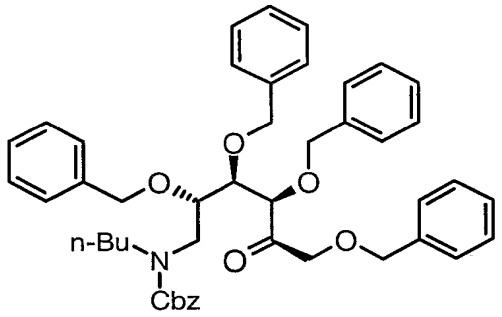
The reactor was loaded with 2,3,4,6-tetra-O-benzyl-D-galactopyranose (540.65 g, 1.00 mol) and sodium cyanoborohydride (69.12 g, 1.1 mol) under an atmosphere of nitrogen. Methanol (1500 mL) and n-butylamine (198.48 mL, 2.0 mol) were added. A mixture of acetic acid (228.72 mL, 4.0 mol) and methanol (300 mL) were added over 30 min at 20-25°C to the yellow solution. Caution: Evolution of hydrogen. The internal temperature was slowly raised to 50°C over 60 min. The reaction mixture was stirred at this temperature until tlc showed the complete consumption of the starting material (about 6-12 h). 1N NaOH (2000 mL) was slowly added to the mixture at 18-25°C. The reaction mixture was extracted with isopropyl acetate (3 x 600 mL). The combined organic layers washed with water (3 x 800 mL) to give the intermediate of formula (V) where R = butyl and P^1 to P^4 = benzyl.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 – 7.34 (m, 20H, 4 x Ph), 4.37 – 4.76 (m, 8H, 4 x CH_2Ph), 3.78 – 4.04 (m, 4H), 3.47 – 3.55 (m, 2H), 2.37 – 2.88 (m, 4H), 1.33 – 1.38 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.21 – 1.31 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.87 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$).

Saturated sodium bicarbonate solution (2000 mL) was added to the isopropyl acetate solution. Benzyl chloroformate (148.04 mL, 1.05 mol) was added slowly over 30 min and the mixture vigorously stirred for 1-2 h until tlc showed complete conversion. The layers were separated. The organic layer was stirred with 30% NaOH (44 mL) for at least 30 min and then diluted with water (960 mL). The organic layer was separated and washed with 1N HCl (1000 mL) and water (2 x 1000 mL). The resulting intermediate of formula (IV) where R = butyl and P^1 to P^4 = benzyl was kept in solution for the next step.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 – 7.41 (m, 25H, 5 x Ph), 4.99 – 5.17 (m, 2H, $COOCH_2Ph$), 4.38 – 4.74 (m, 8H, 4 x CH_2Ph), 3.12 – 4.12 (m, 10H), 1.36 – 1.44 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.13 – 1.27 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.80 – 0.88 (m, 3H, $CH_2CH_2CH_2CH_3$).

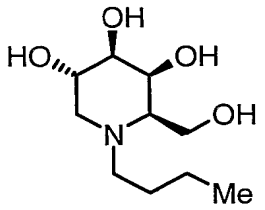
b)



A solution of the product from step a) (731.92 g, 1.00 mol) in isopropyl acetate was concentrated to about 50% of its volume at 300-750 mbar and a jacket temperature of 40-50°C. Isopropyl acetate (950 mL) was added and the solution concentrated again to 50% of its starting volume. The resulting solution was diluted with isopropyl acetate (1250 mL) and concentrated to about 1.8 L/mol at p = 100-300 mbar. The reactor was dried under reduced pressure and loaded with sodium acetate (164.06 g, 2.0 mol) and TEMPO (31.26 g, 0.2 mol) at -5-0°C. The solution of the starting material was added after the reactor had been flooded with nitrogen. A solution of trichloroisocyanuric acid (139.44 g, 0.60 mol) in isopropyl acetate (420 mL) was added slowly over at least 8 h at -5-0°C. After tlc showed complete conversion, the reaction mixture was filtered and precipitate washed with isopropyl acetate (400 mL). The filtrate and washings were combined and then washed with water (2 x 600 mL) and then dried by azeotropic distillation. A second solution of trichloroisocyanuric acid (23.24 g, 0.1 mol) in isopropyl acetate (70 mL) was added slowly over 15 min and then stirred for an additional 15 min. The organic layer was then washed with water (600 mL), saturated sodium hydrogen carbonate solution (2 x 1000 mL) and water (3 x 600 mL). The organic layer was concentrated under reduced pressure (300–750 mbar and a jacket temperature of 40-50°C). Yield of intermediate (II) of formula where R = butyl and P^1 to P^4 = benzyl >85%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 – 7.48 (m, 25H, 5 x Ph), 4.97 – 5.17 (m, 2H, $COOCH_2Ph$), 4.18 – 4.70 (m, 8H, 4 x CH_2Ph), 3.01 – 4.08 (m, 9H), 1.31 – 1.46 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.10 – 1.28 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.78 – 0.87 (m, 3H, $CH_2CH_2CH_2CH_3$).

c)

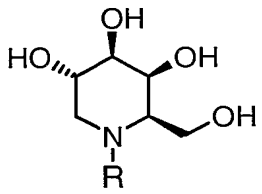


Charcoal (30 g) was added to a solution of the product of step b) (729.90 g, 1.00 mol) in methanol (2700 mL). The mixture was stirred for 15 min and then filtered. The cake was washed with methanol (1000 mL). The mixture was concentrated to a volume of about 1.5 L at 100-500 mbar and a jacket temperature of 40-50°C. This mixture was diluted with methanol (2500 mL) and concentrated again to a volume of about 1.5 L. The mixture was filtered and washed with methanol (1500 mL). Filtrate and washings were further diluted with methanol (5000 mL). The dry and inert reactor was loaded with 10% Pd/C (e.g. Degussa type E1002 NN/W paste 10 %, water content ca. 60%: 146g, 20%w/w). The methanolic solution of the product of step b) was added and the mixture stirred under hydrogen (2 bar) at 18-25°C until the consumption of hydrogen had ceased (ca. 2-4 h). The reactor pressure was then released and hydrochloric acid (32%w/w, 143g) added cautiously over 30 min. The mixture was then stirred under hydrogen (5-6 bar) at 20-25°C until the consumption of hydrogen had ceased (ca. 2-5 h). The mixture was filtered after tlc shows complete conversion and washed with methanol (1200 mL). Caution: The filter cake is pyrophoric and must be kept wet with water. Filtrate and washings were slowly passed through a bed of ion exchanger (ca. 2 L wet, e.g. Amberlite IRA 402) over 3-4 h). The pH of the solution had to be ≥ 8 after leaving the column. Finally, the resin was washed with methanol (2000 mL). This solution was concentrated to about 500 to 750 mL. Charcoal (10 g) was added. The mixture was filtered (0.2 μm), concentrated to an oily residue and toluene added (400 mL). The resulting mixture was dried azeotropically at 100-500 mbar and a jacket temperature of 40-50°C until no more water was observed. The mixture was then concentrated to an oily residue under reduced pressure and a jacket temperature of 40-50°C. To this oily residue was then added acetone (900 mL). The mixture was heated to reflux and water (about 70 mL) was added until a clear solution was obtained. More acetone (1300 mL) was added and the resulting suspension cooled to -15°C over 3 h, filtered, the residue washed with acetone (300 mL) and dried at 35-45°C and 1 to 50 mbar to give 120-150g of the title compound as a white to off-white powder.

^{1}H NMR (D_2O): δ 4.07 (dd, J = 1.7 & 3.4 Hz, 1H), 3.86 (dd, J = 11.5 & 4.5 Hz, 1H), 3.85 (ddd, J = 9.7, 10.7 & 5.0 Hz, 1H), 3.78 (dd, J = 11.5 & 6.7 Hz, 1H), 3.39 (dd, J = 3.4 & 9.7 Hz, 1H), 3.02 (dd, J = 11.4 & 5.0 Hz, 1H), 2.67 (ddd, J = 13.5, 10.2 & 6.1 Hz, 1H, $CH_2CH_2CH_2CH_3$), 2.50 (ddd, J = 6.7, 4.5 & 1.7 Hz, 1H) 2.50 (ddd, J = 13.5, 10.5 & 5.5 Hz, 1H, $CH_2CH_2CH_2CH_3$), 2.21 (dd, J = 11.4 & 10.7 Hz, 1H), 1.46 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.27 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.90 (t, J = 7.4 Hz, 3H, $CH_2CH_2CH_2CH_3$).

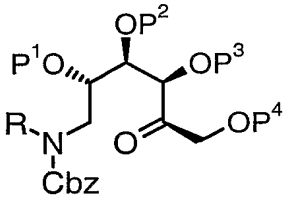
CLAIMS

1. A process for the production of a compound of formula (I):



(I)

wherein R is C_{3-16} straight or branched chain alkyl, optionally substituted by C_{3-7} cycloalkyl, and optionally interrupted by -O-, the oxygen being separated from the ring nitrogen by at least two carbon atoms; or C_{1-10} alkylaryl where aryl is phenyl, optionally substituted by one or more substituents selected from F, CF_3, OCF_3, OR^1, and C_{1-6} straight or branched-chain alkyl; where R^1 is hydrogen, or C_{1-6} straight or branched-chain alkyl; which process comprises reductive ring closure of a compound of formula (II):



(II)

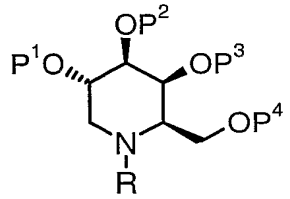
wherein R is defined for formula (I), and P^1 to P^4, which may be the same or different, are benzyl, substituted benzyl or benzylidene protecting groups, followed by deprotection to give the compound of formula (I).

2. The process according to claim 1 wherein R is C_{3-16} straight or branched chain alkyl.

3. The process according to claim 2 wherein R is n-butyl.

4. The process according to any one of the preceding claims wherein P^1 to P^4 are benzyl.

5. The process according to any one of the preceding claims wherein the intermediate compound of formula (III):



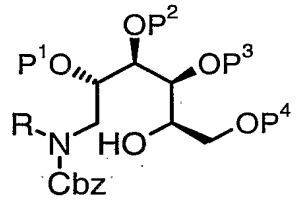
(III)

wherein R and P^1 to P^4 are as defined in claim 1 is not isolated from the reaction but is directly deprotected to give the compound of formula (I).

6. The process according to any one of the preceding claims wherein reductive ring closure of the compound of formula (II) is conducted in the presence of hydrogen gas and a catalyst.

7. The process according to any one of the preceding claims wherein deprotection is conducted in the presence of hydrogen gas and a catalyst in a solvent.

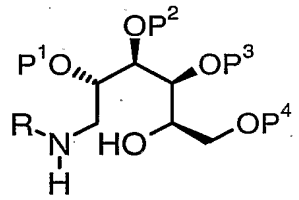
8. The process according to any one of the preceding claims wherein the compound of formula (II) is produced by oxidation of a compound of formula (IV):



(IV)

wherein R and P^1 to P^4 are as defined in claim 1.

9. The process according to claim 8 wherein the compound of formula (IV) is produced by reaction of a compound of formula (V):



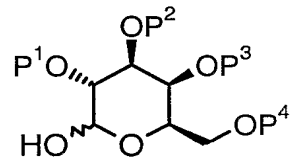
(V)

wherein R and P^1 to P^4 are as defined in claim 1, with a compound of formula (VI):

Cbz-L (VI)

wherein L is a leaving group, in a solvent.

10. The process according to claim 9 wherein the compound of formula (V) is produced by reductive amination of the corresponding protected D-galactopyranose of formula (VII):



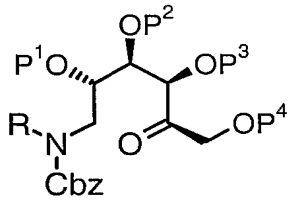
(VII)

wherein P^1 to P^4 are as defined in claim 1, with a compound of formula (VIII):

$R\text{-}NH_2$ (VIII)

wherein R is as defined in claim 1.

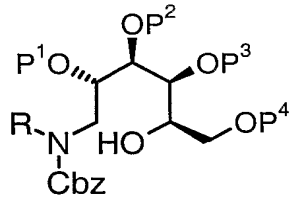
11. A compound of formula (II):



(II)

wherein R and P^1 to P^4 are as defined in claim 1.

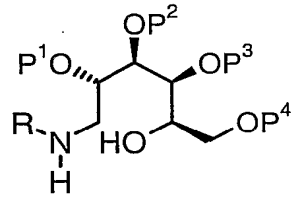
12. A compound of formula (IV):



(IV)

wherein R and P^1 to P^4 are as defined in claim 1.

13. A compound of formula (V):



(V)

wherein R and P^1 to P^4 are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/05528

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/46 C07C271/18 C07C271/16 C07C217/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, PAJ, CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	RICHARD H FURNEAUX ET AL: "Synthesis of 1,5-Dideoxy-1,5-imino-D-galactitol from L-Sorbose" TETRAHEDRON LETTERS, vol. 34, no. 22, 1993, pages 3609-3612, XP002275770 the whole document	1-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2004	16/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/05528

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SAKAE AOYAGI ET AL: "Total synthesis of Galactosidase inhibitors (+)Galactostatin and (+)-1-deoxygalactostatin" JOURNAL OF ORGANIC CHEMISTRY, vol. 56, 1991, pages 815-819, XP002275771 see scheme III	1-13
A	US 4 266 025 A (KINAST GUENTHER ET AL) 5 May 1981 (1981-05-05) the whole document	1-13
A	R BERNOTAS ET AL: "Total synthesis of (+) castanospermine and (+) deoxynojirimycin" TETRAHEDRON LETTERS, vol. 25, no. 2, 1984, pages 165-168, XP001180501 the whole document	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[redacted]ional Application No
PCT/GB 03/05528

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